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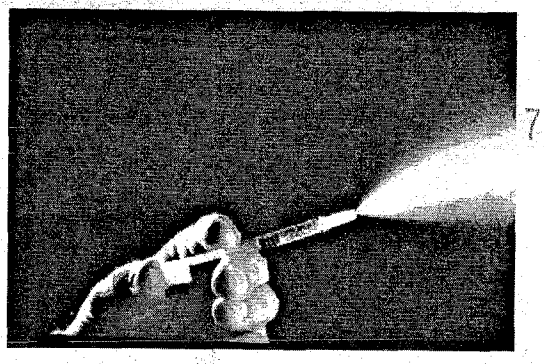

FluMist

An Influenza Vaccine
For Use in Healthy Children
Age 1 – 17

Large Scale Safety in Healthy Children
The Kaiser Study - AV019

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Study Design

Healthy Children AV019

- Randomized, double-blind, placebo-controlled clinical trial
- 2:1 randomization
- Enrollment at 31 Kaiser Permanente sites
- Two doses for healthy children 1-8 years of age given at least one month apart
- One dose for healthy children 9-17 years of age

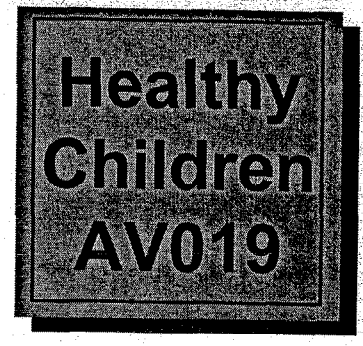
Primary Objective

Healthy Children AV019

To evaluate the safety of FluMist in a large cohort of children by comparing within a 42 day time window the rates in FluMist recipients vs placebo recipients for:

- **Medically attended events (MAEs) - clinic, hospital and Emergency Department (ED) visits**
  - **All observed diagnoses**
  - **Pre-specified grouped diagnoses**
- **SAEs**

Analysis Format
Multiple Comparisons Made



- Utilization setting (ED, clinic, hospital, and combined settings)
- Dose (Dose One, Dose Two, and combined doses)
- By age group (1-17 years, 9-17 years, 1-8 years, 18-35 months, 12-17 months)
- Diagnosis: Comparison made for each diagnosis observed at each site of care
- More than 1,500 comparisons made without statistical adjustments

Enrollment

Healthy Children AV019

- 9689 Total Evaluable Participants

Age in Years	Treatment Group		Total N (%)
	FluMist N (%)	Placebo N (%)	
1-8	3769 (39)	1868 (19)	5637 (58)
9-17	2704 (28)	1348 (14)	4052 (42)
Total	6473 (67)	3216 (33)	9689 (100)

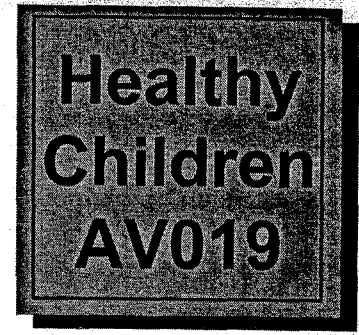
Safety Follow-Up for The Interim Analysis

December 31, 2000

Healthy Children AV019

- All participants had received one dose
  - 88% of Dose One follow-up was complete
- 64% of second dosing was completed
  - 43% of Dose Two follow-up was complete
- Overall, 72% of total expected follow-up for the study was completed

All Diagnostic Categories Observed



- Abdominal Pain
- Abscess
- Acne
- Acute Gastroenteritis
- ADD
- Adenitis/Adenopathy
- Adenoids
- Allergic Enteropathy
- Allergic Reaction
- Allergic Rhinitis/Rhinitis
- Allergy, Food
- Alopecia
- Anemia
- Angioma
- Appendiceal Abscess
- Appendicitis
- Arthritis/Arthralgia
- Asthma
- Atelectasis
- Autism
- Behavioral Disorder
- Benign Lesion
- Bronchiolitis
- Bronchitis
- Cancer, R/O Cancer
- Cellulitis
- Cerebral Palsy
- Chest Pain
- Chlamydia
- Congenital Anomaly
- Congenital heart disease
- Conjunctivitis
- Constipation
- Contact Dermatitis
- Cough
- Croup
- Cyst
- Dehydration
- Dental
- Developmental Delay
- Diarrhea
- Dizziness
- Dysuria
- Eczema
- Elective Procedure
- Enuresis
- Epididymitis
- Epilepsy
- Epiphysitis
- Epistaxis
- Erythema marginatum
- Erythema multiforme
- Eustachian Tube Dysfunction
- Febrile Illness
- Folliculitis
- Foreign Body
- Gallstone
- GE Reflux
- Genital Disorder
- Gingivitis
- Gyn Disorder
- Halitosis
- Headache
- Hearing Loss/Deafness
- Hematochezia
- Hematuria/Proteinuria
- Hemolytic anemia
- Hemolytic Uremic Syndrome
- Hemophilia
- Hepatitis
- Hereditary Spherocytosis
- Herpes Simplex
- Herpes Zoster
- Hilar Adenopathy
- Hives/Urticaria/Angioedema
- HS Purpura
- Hydronephrosis
- Hypercalcinuria
- Hypothyroidism
- Impetigo
- Inflammatory Bowel Disease
- Inguinal Hernia/Repair
- Irritable Bowel Syndrome
- Irritable Child
- Labyrinthitis
- Laryngitis
- Learning Disability
- Migraine
- Molluscum
- Mononucleosis
- Musculoskeletal Pain
- Myokymia
- Nasal Congestion
- Nausea and Vomiting
- Obesity
- Otitis Externa
- Otitis Media
- Otitis Media with Effusion
- Parasite Infestation
- Parotitis
- PE Tubes
- Pharyngitis
- Phimosis
- Pneumonia
- Poisoning/Ingestion
- Pregnancy
- Prematurity
- Psoriasis
- Psychiatric
- Rash
- Respiratory Obstruction
- Scarlet Fever
- Scoliosis
- Seborrhea
- Seizure
- Seizure, Febrile
- Sinusitis
- Sleep Apnea
- Speech Delay
- Speech Disturbance
- Spherocytosis
- Stomatitis
- Syncope/LOC
- T&A
- Testicular Torsion
- Thrush
- Tinea
- Tonsillitis
- Trauma
- Tuberculosis
- Tympanic Membrane Perforation
- Ulcer
- Umbilical Hernia
- Urethral Surgery
- URI
- UTI
- Varicella
- Viral Syndrome
- Vision Disorder
- Warts
- Well Care/Reassurance/FU
- Wheezing
- Xerosis

Percent of Participants Who Experienced an MAE

Healthy Children AV019

Setting	FluMist N = 6473		Placebo N = 3216	
	n	%	n	%
Hospital	23	0.4	14	0.4
ED	141	2.2	75	2.3
Clinic	1812	28.0	905	28.1

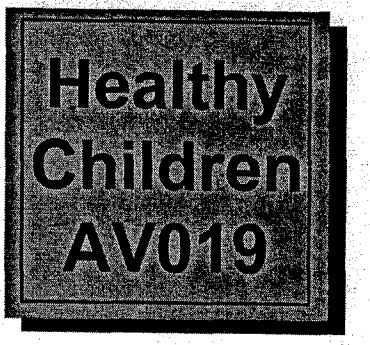
Four Pre-specified Grouped Diagnoses Analyzed

Healthy Children AV019

All settings combined, 1-17 year olds, any dose

Diagnosis Categories	n/N		Rate per 1000 person-months FluMist / placebo	Binomial Relative Risk (90% CI)
	FluMist	Placebo		
Acute Respiratory Tract Events	771 / 6473	387 / 3216	83.6 / 84.2	0.99 (0.90, 1.10) P = 0.900
Systemic Bacterial Infections	0 / 6473	0 / 3216	0.00 / 0.00	- (NA, NA) P = 1.000
Acute Gastrointestinal Tract Events	107 / 6473	65 / 3216	11.6 / 14.2	0.82 (0.63, 1.06) P = 0.209
Rare Events Potentially Related to Influenza	3 / 6473	1 / 3216	0.33 / 0.22	1.5 (0.22, 19.4) P = 0.793

MAEs with Significantly Increased or Decreased Relative Risk



INCREASED Relative Risk	Setting
Abdominal Pain	ED
Asthma	Combined
Conjunctivitis	Clinic & Combined
Otitis Media with Effusion	Clinic
Benign lesion	Clinic
Cellulitis	Clinic
Enuresis	Clinic
Musculoskeletal Pain	Clinic
Otitis externa	Clinic
Seborrhea	Clinic
Speech delay	Clinic
URI	ED
UTI	Clinic

DECREASED Relative Risk	Setting
Abdominal pain	Clinic & Combined
Acute gastroenteritis	Clinic & Combined
Constipation	Clinic & Combined
Cough	Clinic & Combined
Febrile illness	Clinic
Gingivitis	Clinic
Tonsillitis	Clinic & Combined
Trauma	ED & Clinic
Viral syndrome	Clinic
Vision disorder	Clinic
Well care/reassurance/FU	ED
Wheezing	Clinic
Wheezing/SOB	Combined

Evaluation of MAEs with Apparent Increased Relative Risk

Healthy Children AV019

- Evaluation of interval between receipt of vaccine and onset
- Review of prior history of event
- Descriptive review of individual cases from medical records
- Interview of parents for two outcomes:
  - Abdominal pain
  - Conjunctivitis

Conjunctivitis

Healthy Children AV019

- 96 events in 90 patients
  - Incidence = 1.1% in FluMist, 0.7% in placebo
- Elevated in multiple utilization settings, age groups, and doses
  - Clinic and all utilization settings combined
  - Ages 1-17 years, 1-8 years, and 18-35 months
  - Following Dose One and all doses combined

Clinical Features	FluMist (N = 69) %	Placebo (N = 21) %
Concomitant Dx	64	67
Prior History	12	19
Eye Discharge	22	43
Pain	3	5

Conjunctivitis
All Utilization Settings Combined

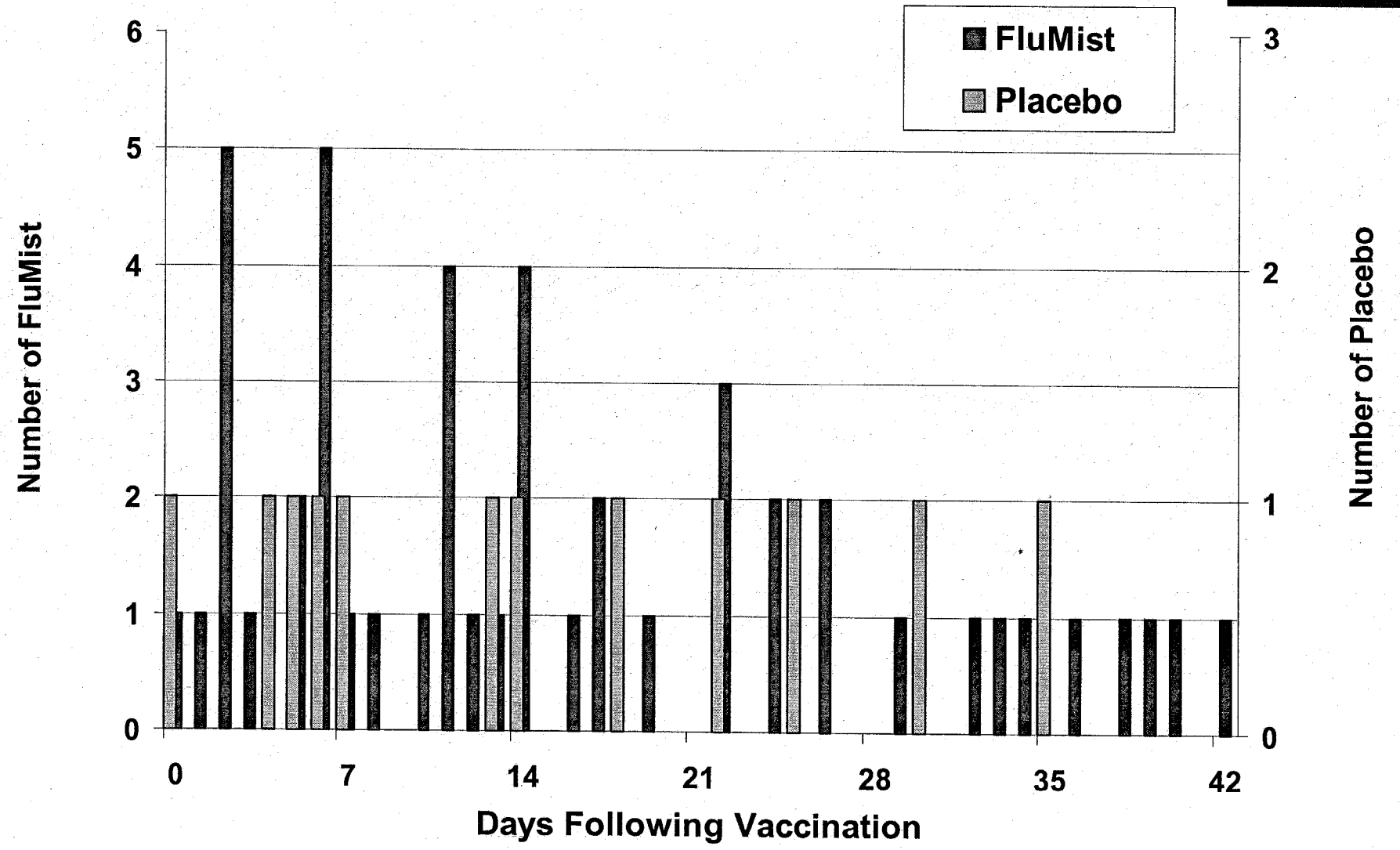
Healthy Children AV019

Age	Dose	n/N		Rate per 1000 person- months FluMist / placebo	Binomial Relative Risk (90% CI)
		FluMist	Placebo		
1 - 17 Years	Combined	69 / 6473	21 / 3216	7.48 / 4.57	1.64 (1.09, 2.50) P = 0.021
1 - 17 Years	One	49 / 6473	12 / 3216	6.73 / 3.32	2.03 (1.21, 3.53) P = 0.011
1 - 8 Years	One	32 / 3769	8 / 1868	8.06 / 4.07	1.98 (1.05, 3.95) P = 0.037
18 - 35 Months	Combined	17 / 728	3 / 369	14.52 / 5.17	2.81 (1.05, 9.07) P = 0.041
18 - 35 Months	One	9 / 728	0 / 369	11.63 / 0	NA (1.74, NA) P = 0.013

Temporal Relationship of Conjunctivitis to Vaccination

All Utilization Settings Combined, 1-17 Years of Age, Following Dose One

Healthy Children AV019



Conjunctivitis: Summary

Healthy Children AV019

- Temporal association with vaccination
- Mild and self-limited with no evidence of any specialty referral or serious sequelae
- Conjunctivitis attributable risk estimated to be 2.8 - 11.6 cases/1000 person-months

Conclusion: There is an apparent low level increased risk of conjunctivitis with receipt of FluMist

Asthma

Healthy Children AV019

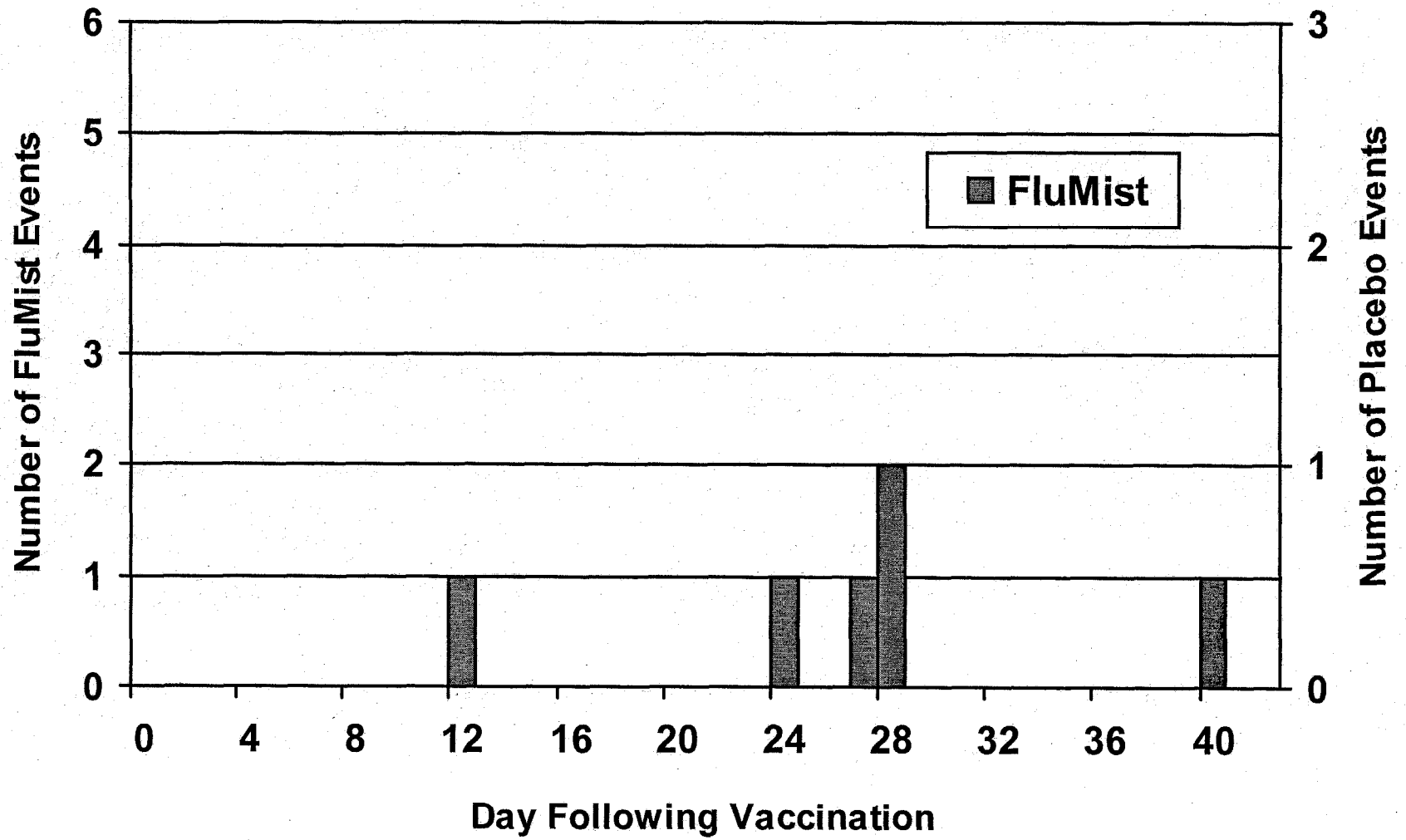
- Elevated in combined settings for 18-35 month olds following Dose One

FluMist Rate n/N = 6/728	Placebo Rate n/N = 0/369	Binomial Relative Risk (90% CI) P value
7.75 cases/1000 person-months	0 cases/1000 person-months	NA (1.08, NA) P = 0.043

Temporal Relationship of Asthma to Vaccination

Combined Settings, 18-35 Months of Age, Following Dose One

Healthy Children AV019



Asthma

Healthy Children AV019

- Of these six patients with asthma:
  - 4 had asthma prior to trial participation
  - 2 had many prior URIs, but no prior asthma diagnosis
    - Onset in these two children was 12 and 40 days after vaccine, respectively

Conclusion: The lack of a consistent temporal relationship with FluMist administration suggests that the increased relative risk for asthma in children 18 - 35 months of age is not related to vaccination.

Otitis Media with Effusion (OME)

Healthy Children AV019

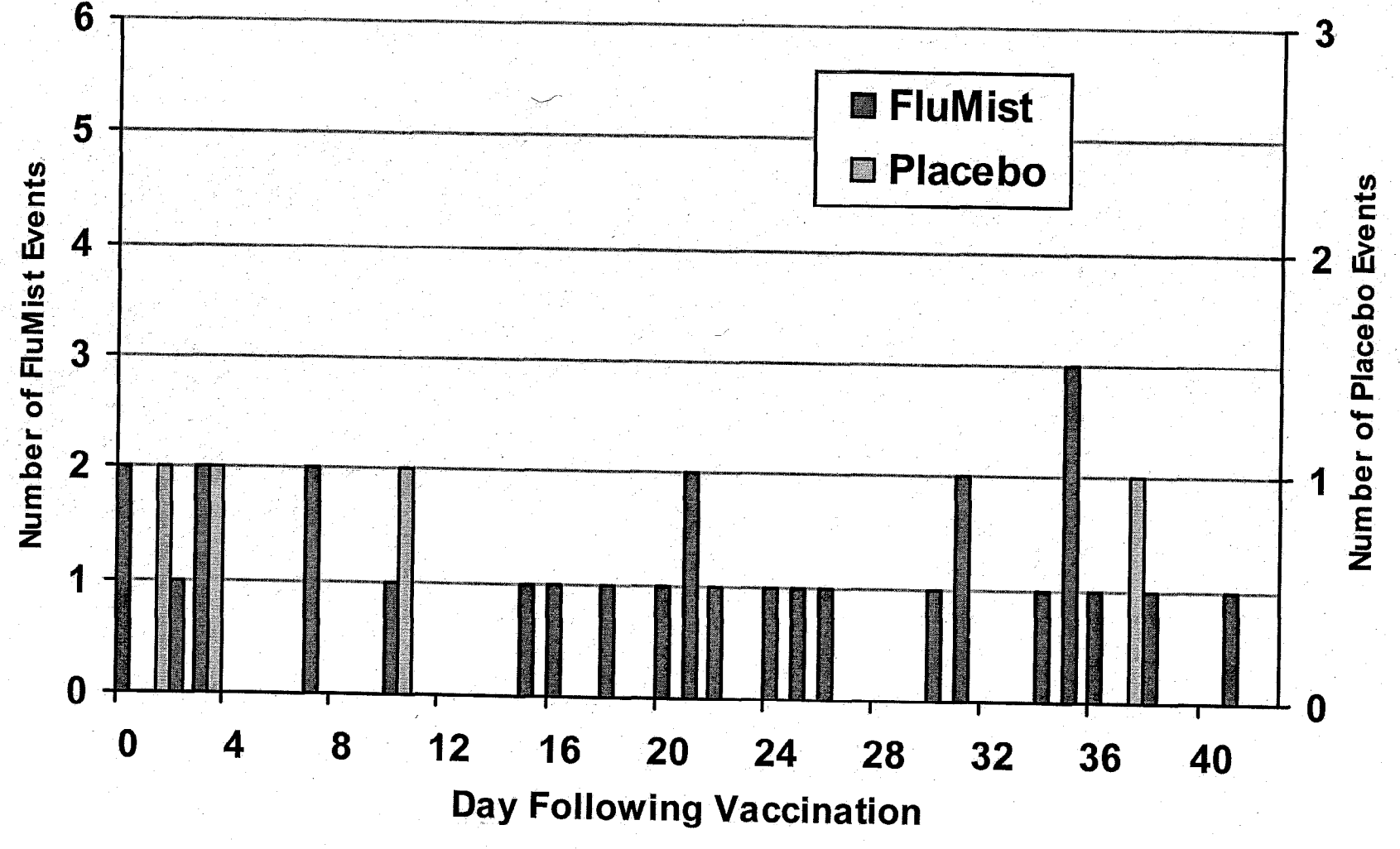
- OME is a chronic form of otitis and is not AOM
- Elevated in clinic setting, 1-8 years of age, following Dose Two only

FluMist Rate n/N = 21/2080	Placebo Rate n/N = 4/1045	Binomial Relative Risk (90% CI) P value
10.79 cases / 1000 person-months	4.09 cases / 1000 person-months	2.64 (1.12, 7.13) P = 0.03

Otitis Media with Effusion

In Clinic, 1 - 8 Year Olds, After Second Dose

Healthy Children AV019



Otitis Media with Effusion: Summary

Healthy Children AV019

- No consistent temporal association with vaccination
- Medical record review revealed a prior diagnosis of OME in:
  - 16 of 21 FluMist recipients
  - 3 of 4 placebo recipients

Conclusion: The nature of a relationship, if any, between OME and FluMist following Dose Two cannot be determined from our results.

Abdominal Pain

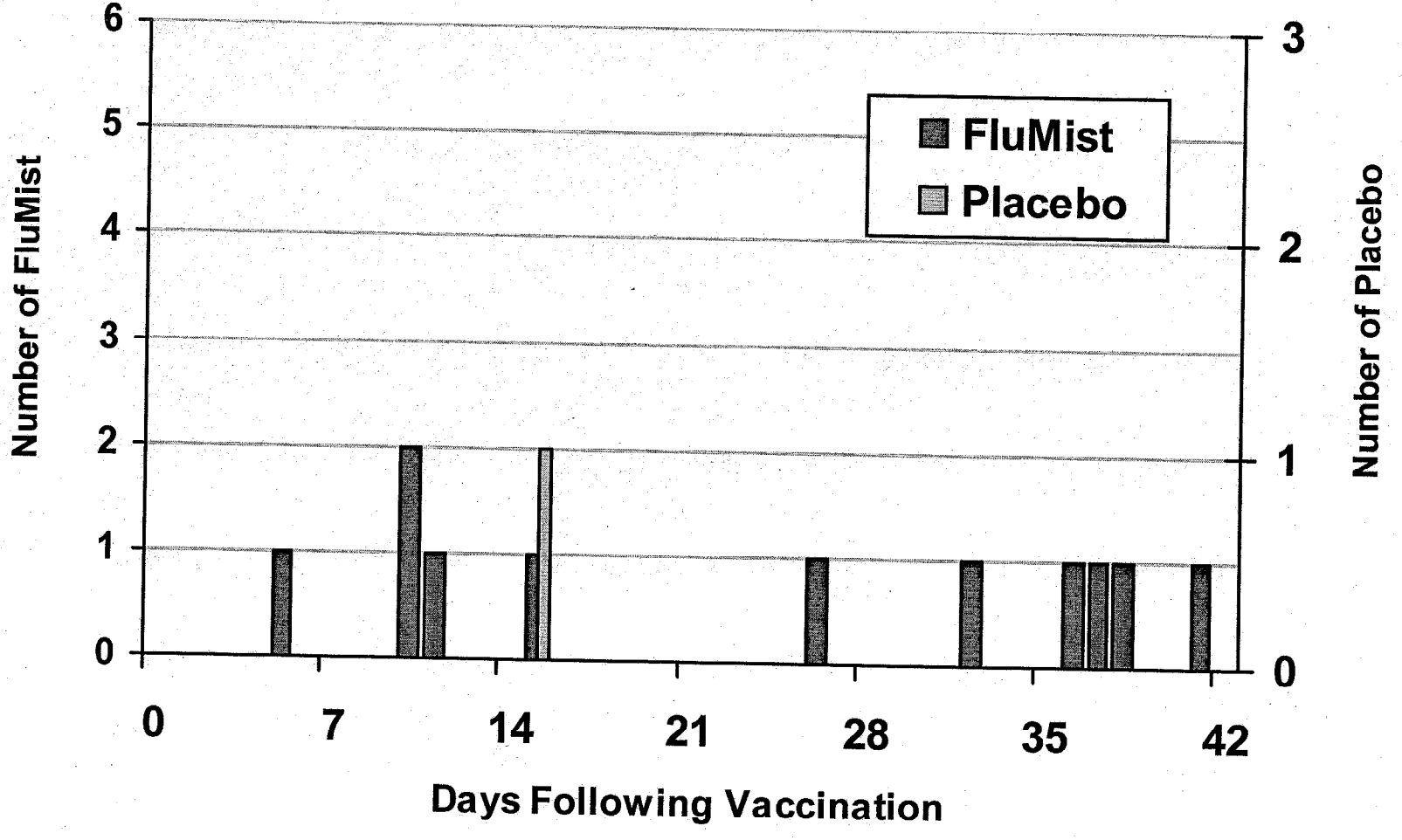
Healthy Children AV019

- Elevated only in one analysis:
  ED, 1-17 years of age, combined doses

FluMist Rate n/N = 11/6473	Placebo Rate n/N = 1/3216	Binomial Relative Risk (90% CI) P value
1.19 cases / 1000 person-months	0.22 cases / 1000 person-months	5.5 (1.2-59.2) P < 0.001

Temporal Relationship of Abdominal Pain to Vaccination ED, 1-17 Years of Age, Combined Doses

Healthy Children AV019



Abdominal Pain

Healthy Children AV019

- Of the 11 cases in FluMist recipients, specific etiologies were subsequently assigned in 4:
  - Pneumonia (+ CXR)
  - UTI (+ urine culture for E. coli)
  - Pain 2° ovulation (due to timing and localization of pain)
  - Pain 2° to stress in family (referred to psychiatry)

Abdominal Pain

Healthy Children AV019

- *Decreased* in three analyses in 1-8 year olds in clinic and combined settings

Setting	Dose	n/N		Rate per 1000 person- months FluMist / placebo	Binomial Relative Risk (90% CI)
		FluMist	Placebo		
Clinic	Combined	8 / 3769	10 / 1868	1.35 / 3.40	0.40 (0.18, 0.88) P = 0.03
Clinic	One	6 / 3769	9 / 1868	1.51 / 4.58	0.33 (0.13, 0.79) P = 0.02
Combined	One	8 / 3769	10 / 1868	2.01 / 5.09	0.40 (0.18, 0.88) P = 0.03

Abdominal Pain

Healthy Children AV019

- **All Settings Combined after All Doses Combined***

Age	Dose	n/N		Rate per 1000 person- months FluMist / Placebo	Binomial Relative Risk (90% CI)
		FluMist	Placebo		
1 – 8 Years	Combined	13 / 3769	11 / 1868	2.20 / 3.74	0.59 (0.30, 1.17) P = 0.203
9 – 17 Years	Combined	20 / 2704	9 / 1348	6.05 / 5.45	1.11 (0.58, 2.22) P = 0.814
1 – 17 Years	Combined	33 / 6473	20 / 3216	3.58 / 4.35	0.82 (0.52, 1.32) P = 0.488

* No hospitalizations observed for this outcome

Abdominal Pain

Evaluation of Diagnoses Associated with Abdominal Pain

Healthy Children AV019

Diagnosis	FluMist (N = 6473) n	Control (N = 3216) n
Appendicitis	1*	0
Negative Laparotomy for R/O appendicitis	1	0
Gastroenteritis	47	28**
Intestinal Obstruction	0	0
Mesenteric Adenitis	0	0
Pancreatitis	0	0

Diagnosis	FluMist (N = 6473) n	Control (N = 3216) n
Perforation	0	0
Ulcer	0	0
Volvulus	0	0
Intussusception	0	0

* Onset of abdominal pain pre-dated FluMist administration

** For gastroenteritis in all settings combined, RR = 0.84

Abdominal Pain: Summary

Healthy Children AV019

- In this study, no consistent clinical presentation or temporal relation to vaccination
- Relative risks were inconsistent
- No evidence of association with potentially serious consequences (intussusception, perforation, etc.)
- However an increased risk was also observed in one prior study

Conclusion: The lack of consistent clinical presentation or temporal relationship observed in this study suggests that abdominal pain in 1-17 year olds in the ED was unrelated to receipt of FluMist

Evaluation of Other Outcomes With Observed Increased Risk

Healthy Children AV019

Outcome	Assessment
Benign Lesion	11 different contributing diagnoses. No consistent body site. No evidence for association.
Cellulitis	▪ Contributing outcomes: Impetigo (21), Cellulitis/Abscess (13), Balanoposthitis (2), Paronychia (2), Plantar Fasciitis (1) ▪ When day zero events excluded, no significant association.
Enuresis	Chronic condition present prior to trial. No evidence for association.
Musculoskeletal Pain	Observed in prior studies. Attributable risk 2.7 - 9.0 cases/1000 persons-months. Consistent with association observed in prior trials.
Otitis Externa	Biological plausibility unlikely. Self limited course. Observed excess risk = 1.5 cases/1000 persons-months
Seborrhea	Chronic condition. Biological plausibility unlikely.
Speech Delay	Six of seven children had diagnosis prior to trial. No evidence for association.
URI	Consistent with association observed in prior trials.
UTI	No consistent time association. Multiple bacterial etiologies. Not consistent with a single pathologic mechanism.

Final Analysis Dataset

Healthy Children AV019

Consistent with prior analysis

- Two new MAEs associated with increased relative risk
  - Elective procedure
  - Warts
- Two MAEs previously associated with increased relative risk were no longer increased
  - Benign lesion
  - Cellulitis
- Eight new MAEs with decreased relative risk were identified

Conclusions

Overall FluMist appeared well-tolerated

- No increased risk in FluMist recipients for any of the pre-specified grouped diagnoses when analyzed in all utilization settings combined
- SAEs occurred at a low rate (0.2%) and none were vaccine related
- Several outcomes observed with elevated risk and biological plausibility: Abdominal pain, asthma, conjunctivitis, otitis media with effusion, musculoskeletal pain, URI
  - Abdominal pain not consistently observed or associated with serious sequelae.
  - Muscle aches, URI-related symptoms observed in previous FluMist trials.
  - Conjunctivitis is associated with receipt of FluMist. Reported as an AE but not statistically associated with vaccine in previous FluMist trials.
    Mild illness in this trial.
- Several biologically plausible outcomes had reduced risk: Acute GI tract events, cough, febrile illness, tonsillitis, viral syndrome, wheezing, shortness of breath